

ARCHE Risk of Bias (ROB) Guidelines

Types of Biases and ROB Domains

Bias	ROB Domain
Selection Bias	Sequence generation Allocation concealment
Performance Bias	Blinding study participants and personnel
Detection Bias	Blinding outcome assessors
Attrition Bias	Incomplete outcome data
Reporting Bias	Selective outcome reporting
Other Bias	“Other sources” of bias

Sequence Generation

- Was the allocation sequence adequately generated?
- Randomization ensures that the groups being compared are balanced for known and unknown confounders.
- Inadequate sequence generation can overestimate treatment effects by 12% (ROR 0.88, 95% CI 0.79, 0.99).¹

ROB Decision	Criteria
Low	Description of a random component in sequence generation process (e.g., computer-generated random numbers, coin toss, random number table).
Unclear	Insufficient data is provided to make a judgment (e.g., only described as: random, randomly generated, randomized, etc.). Statements that groups were blocked or stratified should NOT be considered sufficient for a ‘yes/low risk’ rating unless accompanied by a description indicating the sequence was computer generated,
High	No randomization or inappropriate randomization (e.g. alternation, assignment based on birth date or day of hospital admission).

Allocation Concealment

- Was allocation adequately concealed?
- Allocation concealment ensures that the randomization sequence is unknown to the person entering participants into a trial until allocation to an intervention has occurred.
- Inadequate allocation concealment can exaggerate treatment effects by 18% (ROR 0.82, 95% CI 0.71, 0.94).²

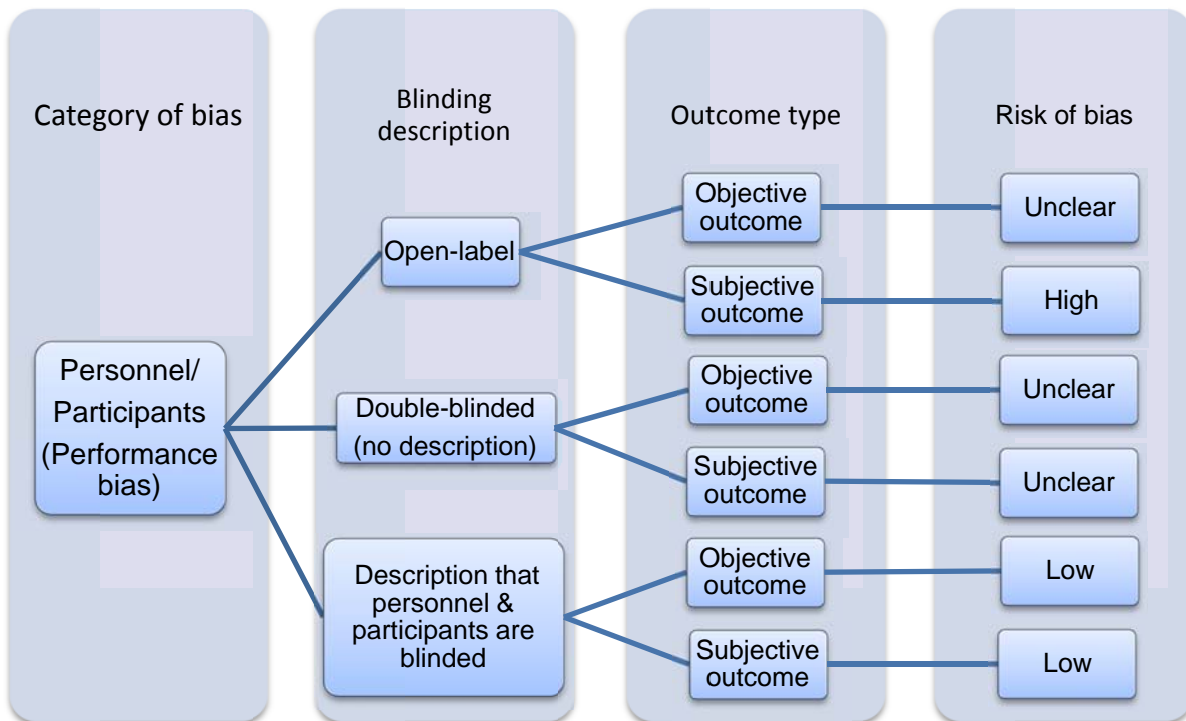
ROB Decision	Criteria
Low	<p>Sequentially numbered, opaque, sealed envelopes.</p> <p>Sequentially numbered drug containers of identical appearance.</p> <p>Central allocation with description (i.e. pharmacy, web-based, call-in).</p> <p>Randomization sequence maintained by a 3rd party uninvolved in the investigation or off-site.</p> <p>Central allocation, but no further description is provided. Use context to determine whether this better fits in 'low' or 'unclear.'</p>
Unclear	<p>No statement.</p> <p>Includes 1 or 2 of: opaque, sealed, sequentially numbered envelopes is described, but does not use ALL 3 descriptors.</p> <p>Randomization sequence is kept on site (with no further description).</p>
High	<p>Open allocation schedule.</p> <p>Any method in which the investigators could foresee the group assignment (e.g. alternation, date of birth, etc.).</p>

Blinding

- Was knowledge of the allocated intervention adequately prevented during the study?
- Blinding of key individuals in a trial can minimize performance and detection bias.
- Studies not described as “double-blind” can overestimate treatment effects by 9% (ROR 0.91, 95% CI 0.83, 1.0).³
- Results not consistent across studies.

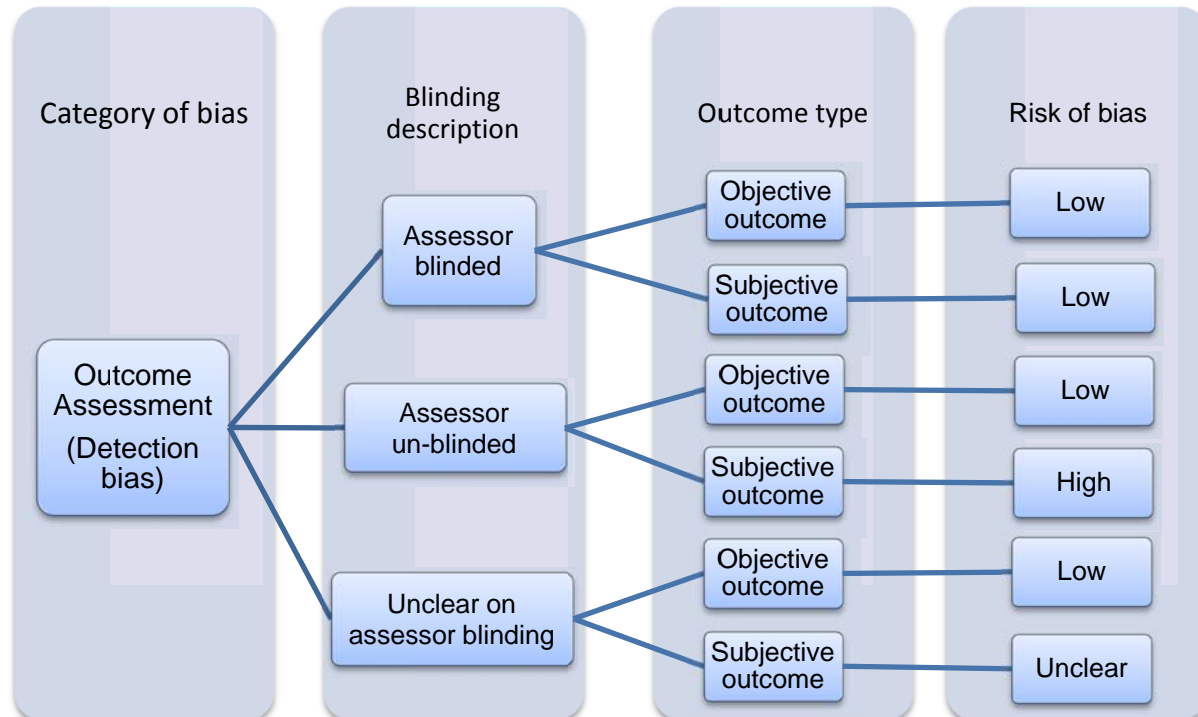
ROB Decision	Criteria
Low	<p>No blinding or incomplete blinding, but the outcome is unlikely to be influenced by lack of blinding.</p> <p>Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.</p> <p>Description of “double-blinding” with specification that the participants and study personnel are blinded.</p> <p>Description of the use of “double-dummy” or “matched placebo.”</p>
Unclear	<p>Insufficient information to permit judgment.</p> <p>The study did not address blinding.</p>
High	<p>No blinding or incomplete blinding and the outcome is likely to be influenced.</p> <p>Blinding attempted, but likely that it could have been broken and the outcome is likely to be influenced.</p>

Blinding of participants and personnel (Performance bias)



Blinding of outcome assessment (Detection bias)

- Used when 3rd party assessor is mentioned.
- When 3rd party assessor is not mentioned, use the same assessment as for blinding of participants and personnel.



Incomplete Outcome Data

- Were incomplete outcome data adequately addressed?
- Per protocol analyses may yield more favourable estimates compared to intention-to-treat (ITT) analyses.
- “Modified” ITT* may overestimate treatment effects by 15% (ROR 0.85, 95% CI 0.81, 0.88).⁴
- Results not consistent across studies.

ROB Decision	Criteria
Low ROB	ITT and dropout rate <10%. No ITT, dropout rate <10%, and number and reasons for withdrawal balanced between groups.
Unclear ROB	ITT and/or dropout rate between 10 and 30%.
High ROB	Dropout rate ≥30%. Dropout rate <30%, but number and reason for dropouts very imbalanced between groups. Per protocol analysis only (unless under of patients switching groups is too

small to make any important difference to the estimated intervention effect).

*Modified ITT is not consistently defined, but may refer to how participants contribute outcome data (e.g., all participants available for follow-up at timepoint X), and whether all or a subset of randomized participants are included in the analysis (e.g., excluding participants that did not receive a specified minimum amount of the intended intervention). In assessing this domain, closely consider the description of what was done, the dropout rate, and the likelihood for bias.

Selective outcome reporting

- Is there an indication that the reports are free of selective outcome reporting (SOR)?
- SOR occurs when a subset of the original variables recorded for investigation in the protocol is presented in the publication.
- It may also be indicated by discrepancies in the primary outcomes proposed and those reported.
- Statistically significant outcomes are more likely to be completely reported than non-significant outcomes (range of odds ratios 2.2 to 4.7).⁵

ROB Decision	Criteria
Low ROB	No discrepancies between outcomes listed in the protocol and those described in the results. No discrepancies between methods section and results section in the study report(s).
Unclear ROB	N/A
High ROB	Outcomes are identified in the protocol or methods section that are not described in the results section of the report.

When to search for protocols:

Cochrane recommendations	Protocol should be compared with results. In a previous study, we found that searching for protocols had little yield, but often changed assessment when found.
Protocol or registry number is reported	Look for the protocol and compare outcomes in protocol with the results. Protocol registries: clinicaltrials.gov, ISRCTN, WHO, Australia/New Zealand registry
No protocol reported	Do not look for protocols. Compare the methods section with the results for: primary vs. secondary outcomes; first outcome reported in methods vs. first outcome reported in results; time points of outcome assessment

Request guidance from clinical leads to determine if there are key outcomes that should be reported according to the report topic. Decisions on searching for protocols and how to use them should be made at the outset of each review, based on the specific context.

Other sources of bias

- “Catch-all” domain.
- Source of funding or early stopping should not be assessed in “other sources” of bias; however, continue to extract these items and report them in the results/discussion sections.
 - Conduct a sensitivity analysis for studies that received industry funding versus no industry funding.
 - Conflict of interest can be assessed in the “publication bias” domain of GRADE.
- Specific “other sources” of bias will not be identified to assess for each project.

ROB Decision	Criteria
Low ROB	No other sources of bias are identified. This is the default assessment.
Unclear ROB	N/A
High ROB	Other sources of bias such as: participant characteristics (baseline imbalances), study design characteristics (crossover, cluster randomized, blocked randomization in unblinded trials).

Overall ROB Assessment

ROB Decision	Criteria
Low ROB	All domains are assessed as low.
Unclear ROB	At least one domain is assessed as unclear and no domains are assessed as high.
High ROB	At least one domain is assessed as high.

¹ Als-Nielsen B, Gluud LL, Gluud C. Methodological quality and treatment effects in randomised trials: a review of six empirical studies. 12th Cochrane Colloquium Oct 2-6, Ottawa, Ontario, Canada, 2004

² Pildal J, Hrobjartsson A, Jorgensen KJ, Hilden J, Altman DG, Gotzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. Int J Epidemiol 2004; 36(4):847-457

³ Pildal J, Hrobjartsson A, Jorgensen KJ, Hilden J, Altman DG, Gotzsche PC. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. Int J Epidemiol 2004; 36(4):847-457

⁴ Abraha I, Duca PG, Montedori A. Empirical evidence of bias: modified intention to treat analysis of randomised trials affects estimates of intervention efficacy. Z Evid Fortbild Qual Gesundheitswes 2008; 102[Suppl VI]:9.

⁵ Dwan K, Altman DG, Arnaiz JA, Bloom J, Chan AW, Cronin E, et al. Systematic review of the empirical evidence of study publication bias and outcome reporting bias. PLoS ONE 2008; 3(80):e3081.